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EXAMINER	
GANGLE, BRIAN J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,655	DIDEBERG ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-52 and 55-59* is/are rejected.

7)☒ Claim(s) *53, 54, 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks, filed on 7/10/2007 and 10/2/2007, are acknowledged.

Claims 1-48 are cancelled. Claims 49-60 are added. Claims 49-60 are pending and are currently under examination.

The declaration, under 37 CFR 1.132, filed 7/10/2007, by Thierry Vernet, has been considered.

Objections Withdrawn

The objection to the disclosure, because it contains an embedded hyperlink and/or other form of browser-executable code on page 3, is withdrawn in light of applicant's amendment thereto.

The objection to claim 48 because the claim is drawn, in part, to non-elected subject matter is withdrawn. The cancellation of the claim renders the objection moot.

New Objections

Claim 50 is objected to because of the following informalities: the claim contains the phrase "selected in one or both groups." The claim should state, "selected from one or both groups." In addition, part (b) contains the word "relataive." Presumably, the word should be "relative." Appropriate correction is required.

Claim 53 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The protein of this claim, with the sequence of SEQ ID NO:1 is free of the art of record.

Claim 58 is objected to because of the following informalities: the structure of the sentence and usage of commas is incorrect. If applicant intends the PBP2x protein to have a sequence which is at least 50% identical to the sequence of SEQ ID NO:18 and to be encoded by the *pbpX* gene, there should be a comma between the word "protein" and the word "which" in line 2.

Claims 54 and 60 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Rejections Withdrawn

The rejection of claims 23-26, 28-33 and 48 under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling, is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claims 23-26, 28-33 and 48 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claims 23-26, 28-33 and 48 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant protein which has the sequence of SEQ ID NO:1, does not reasonably provide enablement for the claims as drawn is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claim 23, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "a recombinant protein obtained from *Streptococcus pneunoniae* PBP2x protein, which recombinant protein comprises concatenated fragments corresponding, respectively, to amino acids located between positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750" is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 23, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the terms SWISSPROT p14677 and GENBANK 18266817 is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 24, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "wherein the peptide fragment comprises amino acids of said Streptococcus pneumoniae PBP2x protein located between positions -1 to -7, relative to the residues at positions 74, 186, 218 and 257, or between positions +1 to +7, relative to the residues at positions 90, 199 and 228, as defined in claim 23, or both" is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 25, under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "amino acids comprising alanine, serine, glycine and threonine or a combination thereof" is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 33 under 35 U.S.C. 102(e), as being anticipated by Doucette-Stamm *et al.* (US Patent 6,699,703, filed 5/2000), is withdrawn. The cancellation of said claim renders the rejection moot.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-52 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The instant claims are drawn to a recombinant protein derived from a PBP2x protein of *Streptococcus pneumoniae*, which recombinant protein comprises concatenated peptide fragments of said PBP2x protein, wherein the sequence of each one of said peptide fragments, in the orientation from the N-terminus to the C-terminus of the recombinant protein, is that situated, respectively from positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750 of said PBP2x protein amino acid sequence and wherein each one of said peptide fragments is preceded by a linking peptide of 1 to 7 amino acids. The claims further include said recombinant protein where the *Streptococcus pneumoniae* PBP2x protein has at least 50% identity, or is at least 85% similar with the sequence of SEQ ID NO:18.

The specification discloses SEQ ID NO:1, which is the sequence of a recombinant protein meeting the limitations of the claims, and which meets the written description requirements. However, the instant claims are drawn to a vast genus of proteins that do no not meet the written description requirements and that have no correlation between their structure and function. Furthermore, the specification only describes the sequence of one PBP2x protein (SEQ ID NO:18). The claims require specific residues in said sequence, but refer to any PBP2x sequence, of which there are many. In addition, the aforementioned claims encompass recombinant proteins which require specific residues from a protein which has only 50% homology to the PBP2x protein.

To fulfill the written description requirements set forth under 35 USC 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession of the claimed invention.

The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid and/or protein itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Therefore, only SEQ ID NO:1, but not the full breadth of the claims, meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-

Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Applicant's arguments regarding the previous written description rejection that are applicable are addressed here.

Applicant argues:

1. That it is clear from the specification that PBP2x is a well-known protein and numerous sequences of this protein from different *S. pneumoniae* isolates are available in th art. Applicant asserts that the structure, including the 3D structure, as well as the structure-function relationship of the PBP2x protein have been determined.

2. That the sequence of the PBP2x from other isolates may be obtained by conventional techniques known in the art.

3. That the present application discloses the amino acid sequence of the four fragments of the PBP2x protein from *S. pneumoniae* strain R6 and their position relative to the PBP2x amino acid sequence.

4. That the PBP2x protein is very conserved with 86% identity.

5. That the skilled artisan could easily obtain the sequence of the four fragments of the claimed protein for any PBP2x protein.

6. That the sequence of the linking peptide is specified in the application.

7. That, as argued above, the claimed protein contains "four completely defined fragments of a protein whose sequence, structure, and structure-function relationship are well known, and each fragment is preceded by a linking peptide whose sequence is specified in the instant application."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the examiner agrees that there are many PBP2x proteins known in the art and the sequences for many of these are available in various databases. In general, the structure-function relationship of these has been elucidated. However, it is well known in the art that protein function is dependent on the three-dimensional shape of the protein. Changes of even a single amino acid can drastically alter the activity of a protein and the effects of a given change are unpredictable (see Bowie *et al.*, Lazar *et al.*, and Burgess *et al.*). While the structure-

function relationship of a full-length PBP2x protein may be known, it is not known, and applicant has not demonstrated, that portions of the PBP2x protein with various linkers will function in the same manner. When one looks at the possible linking peptides encompassed by the claims, one can see that the claims encompass more than 5 *billion* possible proteins. The specification shows one. Changes in any of these linkers could lead to drastic alterations in the protein's function. Furthermore, the single example shown in the specification is taken from a version of PBP2x that is sensitive to β-lactams. The claims encompass both resistant and sensitive versions of the protein. However, to become resistant, the protein must undergo mutation. The specification does not describe any possible mutations or how these mutations would affect the recombinant protein. In addition, the claims require that the concatenated fragments be from specific residues of the PBP2x protein. However, while one of skill in the art might be able to determine which conserved portions of PBP2x are required, the claims do not require these portions. They require specific portions, set forth as residues 74-90, 186-199, 218-228, and 257-750. If the PBP2x protein parent has different numbering, or does not align in the same manner as the R6 strain shown in the specification, one would end up with a recombinant protein whose function is wholly unrelated to the claimed invention. This is exemplified in the examples of PBP2x proteins applicant has submitted. The PBP2x protein with the accession number AAY56845.1 has, at position 82, the amino acid that is position 1 of the R6 strain. This means that the portions between positions 74-90, etc., will be completely different.

Regarding argument 2, applicant is reminded that written description requires more than a mere statement that something is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The question with written description is whether applicant had possession of the claimed invention. Clearly, applicant did not have possession of the more than 5 billion proteins encompassed by the claims, and there is no defining feature that would allow the single disclosed embodiment to be representative of the large and variant genus.

Regarding argument 3, the specification does disclose the amino acid sequence for the concatenated fragments of the PBP2x from *S. pneumoniae* strain R6. The corresponding

recombinant protein is shown in SEQ ID NO:1, and meets the written description requirements. However, as stated above, these fragments (defined by amino acid residue numbers) are not applicable to all PBP2x proteins. Furthermore, the linking peptides are not defined, and as is well known in the art (see above) altering these linkers can alter the conformation and the function of the protein. Thus, only the PBP2x protein disclosed as SEQ ID NO:1 meets the written description requirements.

Regarding argument 4, while applicant states that the PBP2x protein is conserved with 86% identity, the claims specifically encompass PBP2x proteins with only 50% identity to that of strain R6. There is no description in the specification or the art of a protein that has the function of a PBP2x protein, but that has only 50% homology to that of the R6 strain.

Regarding argument 5, as stated above, written description requires more than a mere statement that something is part of the invention and reference to a potential method for isolating it. Moreover, the four fragments are defined by the numbers of the amino acids and not by a function. As discussed above, different PBP2x proteins have different numbering; therefore, while the fragments could be obtained, there is nothing to imply they would have a function even remotely similar to that of SEQ ID NO:1.

Regarding argument 6, the sequence of *a* set of linking peptides is specified in the application. The language of the claims (i.e. 1-7 amino acids) is such that the claims encompass more than 5 billion variants. Only one of these has been shown to perform the function that applicants envision.

Regarding argument 7, as stated above, neither the fragments nor the linking peptides are "completely defined." There is no disclosed correlation between the structure of these proteins and their function, and applicant has not shown possession of the enormous genus encompassed by the claims.

Regarding the declaration by Thierry Vernet, the statements in the declaration correspond to the arguments set forth above. In addition, Dr. Vernet states "the specification provides a written description for the claimed recombinant protein. According to MPEP 716.01(c), an opinion as to a legal conclusion is not entitled to any weight. The facts used by applicant to reach this conclusion have been addressed above.

Claims 49-52 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant protein which has the sequence of SEQ ID NO:1, does not reasonably provide enablement for a recombinant protein derived from a PBP2x protein of *Streptococcus pneumoniae*, wherein said protein comprises concatenated peptide fragments of said PBP2x protein, wherein the sequence of each one of said peptide fragments is that situated, respectively, from positions 74-90, 186 to 199, 218 to 228, and 257-750 of said PBP2x protein amino acid sequence and wherein each one of said peptide fragments is preceded by a linking peptide of 1 to 7 amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to a recombinant protein derived from a PBP2x protein of *Streptococcus pneumoniae*, which recombinant protein comprises concatenated peptide fragments of said PBP2x protein, wherein the sequence of each one of said peptide fragments, in the orientation from the N-terminus to the C-terminus of the recombinant protein, is that situated, respectively from positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750 of said PBP2x protein amino acid sequence and wherein each one of said peptide fragments is preceded by a linking peptide of 1 to 7 amino acids. The claims further include said recombinant protein where the *Streptococcus pneumoniae* PBP2x protein has at least 50% identity, or is at least 85% similar with the sequence of SEQ ID NO:18. These claims encompass a vast genus of polypeptides that have no correlation between their structure and a specific function. Furthermore, the specification only describes the sequence of one PBP2x protein (SEQ ID NO:18). The claims require specific residues in said sequence, but refer to any PBP2x sequence, of which there are many. In addition, the aforementioned claims encompass recombinant proteins which require specific residues from a protein which has only 50% homology to the PBP2x protein. The specification does disclose SEQ ID NO:1, which meets the limitations of the claims.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence

encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess *et al.* (J. of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar *et al.* (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, fragments of PBP2x that maintain the function of PBP2x could not be predicted. Additionally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3).

Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie *et al.*, Lazar *et al.* and Burgess *et al.* but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the claimed proteins could not be predicted based on sequence identity to PBP2x. Clearly, it could not be predicted that polypeptide or a variant that shares only partial homology with a disclosed protein will function in a given manner (i.e. PBP2x carboxypeptidase activity). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus of proteins. In view of the above, one of skill in the art would be forced into undue experimentation to practice the full scope of the claimed invention. Therefore, only the recombinant protein with the sequence of SEQ ID NO:1 is enabled.

Applicant's arguments regarding the previous written description rejection that are applicable are addressed here.

Applicant argues:

1. That the portion of PBP2x that represents the major target for identifying novel antibiotics is intact in the recombinant protein of the invention and that example 2 clearly demonstrates that the enzymatic activity of PBP2x protein is present in the recombinant protein.

2. That, since all of the PBP2x proteins from different strains are very conserved and share the same structure which corresponds to the same function, it is considered that similar results would be obtained with any PBP2x protein. Applicant argues that, because of this, the

results shown in example 2 are representative of all of the recombinant proteins encompassed by the claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the examiner agrees that the protein shown in example 2 contains the portions of PBP2x that are necessary for activity, and this protein (with the sequence of SEQ ID NO:1) is enabled by the specification. However, applicant's assertion that the portion of PBP2x that represents the major target for identifying novel antibiotics is intact in the recombinant protein of the invention, is incorrect. The claims require specific portions of the PBP2x protein that are not defined by their function, but by the amino acid positions. As seen in several of the PBP2x proteins found in the art (the PBP2x protein with the accession number AAY56845.1, for example), the numbers required by the claims do not correspond to the same portions of the protein. Therefore, the portions of the protein required by the claims would not have the same function as the protein shown in example 2.

Regarding argument 2, as discussed above, while the known PBP2x proteins may be highly conserved, they do not all have the same corresponding portions at the same position numbers. Furthermore, changes of a single amino acid can alter the folding and thus, the function of a protein. Therefore, there is no way to know that the proteins encompassed by the claims will behave in the same manner. Furthermore, it is well established in all fields of science that a single sample is not representative of an entire population. In the instant case, one would not expect a single protein to be representative of the billions of proteins encompassed by the claims.

Regarding the declaration by Thierry Vernet, the statements in the declaration correspond to the arguments set forth above. In addition, Dr. Vernet states "the specification enables any person skilled in the art to make and use the invention commensurate in scope with the instant claims. According to MPEP 716.01(c), an opinion as to a legal conclusion is not entitled to any weight. The facts used by applicant to reach this conclusion have been addressed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50, 58, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 is rendered vague and indefinite by the phrase "wherein the linking peptide comprises 1 to 7 amino acid residue(s)." The parent claim requires linking peptides that are 1 to 7 amino acids in length. However, claim 50 is drawn to a protein where the linking peptides *comprise* 1 to 7 amino acids. Since the parent claim limits the linking peptides to 7 amino acids, the dependent claim cannot have linking peptides that are more than 7 amino acids. Furthermore, the protein of the parent claim contains multiple linking peptides, whereas claim 50 refers to "the linking peptide." It is not clear which of the linking peptides claim 50 is referring to.

Claim 58 (and dependent claim 59) is rendered vague and indefinite by the use of the word "similar." The specification, on page 7, states that "the similarity of a sequence relative to a reference sequence is assessed as a function of the percentage of amino acid residues which are identical or which differ by conservative substitutions, when the two sequences are aligned so as to obtain the maximum correspondence between them." The specification defines the term "conservative substitution" as "the substitution of an amino acid with another which has similar chemical properties (size, charge or polarity), which generally does not modify the functional properties of the protein." Therefore, it is not clear what is encompassed by the term "similar." What degree of similarity makes an amino acid "similar"? Which amino acids will not "generally" modify the functional properties of the protein?

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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